In a telephone interview with Examiner Nutter on April 10, 1992, it was determined that the withdrawal of claim 22 from consideration was an inadvertent oversight by the Examiner, that claim 22 was deemed to read on the elected species, and that claim 22 should be reinstated and considered as a claim drawn to the elected species. Accordingly, Applicants understand that claims 21-26, 28, 29, 34, 35, 45, 46, 50, 51, and 81-86 are currently under consideration in this application. Following this amendment, claims 22-26, 28, 29, 34, 35, 45, 50, 51, 81, 82, 85 and 86 will be under consideration. Should the genus be found allowable, Applicants understand that claims 32, 33, 36-44 and 87-95 will be considered.

The title has been amended to read "Osteogenic Proteins" in response to the Examiner's request that the title more particularly describe the invention claimed in the instant application.

Applicants' invention, in its broadest aspects, is based on the discovery of the most fundamental amino acid sequence structure required for osteogenic activity. The present invention is a continuation-in-part of U.S. Application Serial No. 179,406, now U.S. Patent No. 4,968,590, wherein Applicants disclosed how to make substantially pure osteogenic protein having a half maximum bone inducing activity of at least about 25 to 50 ng per 25 mg of matrix. Elucidation of the amino acid sequence and investigation of the properties and structure of the native form osteogenic protein has allowed Applicants to identify a critical amino acid sequence structure, including specific, required amino acids, which characterize the amino acid sequence of chondrogenic and osteogenic proteins. Identification of this critical sequence allowed Applicants to identify osteogenically active sequences from sequences in the art not previously identified as osteogenically active, and to design a "consensus"

gene sequence with which to probe genetic libraries for novel DNA sequences encoding osteogenic proteins. For example, the consensus gene sequence led to isolation of each of the DNA sequences encoding each of the polypeptides of the natural-sourced osteogenic protein's two chain sequence. The DNA sequences encode novel polypeptides designated as OP-1 and CBMP2. The DNA sequence of CBMP2 corresponds to a subregion of the BMP2 DNA sequences disclosed by Wang et al. in PCT publication WO 88/00205. The sequence of OP-1 has never before been described as far as Applicants are aware. Moreover, using the protocol described in the instant application, Applicants subsequently have identified still another novel sequence, referred to as OP-2 and disclosed in co-pending USSN 599,543, filed October 18, 1990, and USSN 841,646, filed February 21, 1992. In addition, murine analogs of both OP-1 and OP-2 also have been identified using this methodology.

In addition, design of the consensus sequence and comparison of this sequence with OP-1 and CBMP2 has permitted Applicants to develop a rational design for novel, biosynthetic, non-native proteins, i.e., forms never before known in nature, capable of inducing endochondral bone and/or cartilage formation in a mammal. As far as Applicants are aware, the biosynthetic constructs of this invention constitute the first instance of the design of a functional osteogenically or chondrogenically active protein without preexisting knowledge of the active region of a native form nucleotide or amino acid sequence. Using the rational design, Applicants synthesized a number of non-native DNA sequences designated COP1, COP3, COP4, COP5, COP7 and COP16, and demonstrated bone formation activity for the expression products of COP5 and COP7. Subsequent work has shown that COP16 (WO89/01469) and truncated and full length forms of OP-1 also induce endochondral bone formation (WO 89/10649, USSN 810,560, and USSN 841,464.)

Applicants also disclose active sequences found in nature, e.g., Vgl and DPP, none of which have been described previously as capable of osteogenic activity or linked with such activity. CBMP2b and CBMP3, both of which correspond to subregions of genomic DNA and/or cDNA sequences disclosed in WO 88/00205, also have not been shown to have bone forming activity prior to Applicants' invention.

Applicants' claims therefore are properly directed to structures embodying the generic amino acid structure required for bone-inducing activity and seek to protect this generic invention. Accordingly, Applicants have defined the required structure generically. Specifically they have identified the apparently critical amino acids and their position within the sequence, and have allowed the remaining residues to be any amino acid, provided that the final material, when dimerized, disulfide bonded and implanted together with a suitable matrix, has a conformation capable of inducing endochondral bone (or cartilage) formation in a mammal. Applicants also define the invention as including dimeric proteins wherein the amino acid sequence of each subunit is sufficiently duplicative of either of the novel, non-native sequences COP5 or COP7, both of which were created based on the generic sequence formula of Applicants' invention and Applicants' rational design for creating non-native osteogenic sequences. As described in the application and defined in the claims, "sufficiently duplicative" requires that the claimed dimeric protein, when its subunits are dimerized, disulfide bonded and implanted in a mammal in association with a suitable matrix, have a conformation capable of inducing endochondral bone (or cartilage) formation in that mammal.

Reconsideration and withdrawal of the various rejections is requested in view of the amendments and the remarks which follow.

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Objection to the Specification Under 35 USC §112

The specification currently is objected to under 35 USC §112, first paragraph, and the pending claims rejected therefore, as failing to provide an adequate written description of the invention. The Examiner asserts that the specification fails to disclose specifically what may be embraced by each representation of "X" as amino acids.

Applicants respectfully traverse this rejection and submit that the specification as filed complies fully with both the "written description of the invention" requirement and the "enablement" requirement under 35 USC §112, first paragraph.

Applicants have discovered the amino acids and linear sequence necessary for bone forming and cartilage forming activity. This discovery has allowed them to design a generic amino acid sequence wherein certain residues are predetermined and certain other residues may be varied. An "X" is provided at the positions within the generic sequence where the amino acid residue may be varied to indicate that there are no a priori limitations on the amino acids selected for each of these positions, provided that the final product, as part of a disulfide bonded dimeric species, is capable of inducing endochondral bone (or cartilage) formation when implanted in a mammal in association with a matrix.

As described in the specification, each presentation of "X" in the generic sequence formula independently represents an amino acid. The Examiner is directed to p.10, lines 6-7, and p.62, lines 15-16 and lines 24-25 of the specification, where "X" is disclosed as representing a single amino acid residue. Accordingly, as described in the specification and defined in the claims, each "X" in the generic sequence may be any one of the known amino acids, provided that the resulting polypeptide chain,

when combined with a second polypeptide chain and disulfide bonded to produce a dimeric species, comprises part of a dimeric protein having a conformation capable of inducing bone (or cartilage) formation when implanted in the mammal in association with a suitable matrix.

The "written description" requirement of 35 USC §112, first paragraph, requires that the Applicant "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." Vas-Cath Inc. v. Mahurkar 19 USPQ2d 1111, 1117 (CAFC, 1991) (emphasis in the original.) Applicants respectfully submit that the specification, as filed, adequately describes Applicants' invention. Moreover, while exact correspondence between the claim language and the specification is not required, such correspondence is normally found to satisfy the description requirement. In re Smith and Hubin 481 Fed.2d 910, 914 (CCPA, 1973).

Applicants also respectfully submit that the specification is sufficient to enable one of ordinary skill in the art to make, test and use the proteins of this invention without undue experimentation, and complies fully with the enablement requirement of 35 USC §112, first paragraph. See In re Angstadt and Griffin 190 USPQ 214 (CCPA, 1976).

The Examiner is directed to pp. 26-37 of the specification where a detailed description of how to obtain native osteogenic protein from natural sources is disclosed, and to pp. 38-52 of the specification, where a detailed description of the functional, structural and biochemical characterization of the natural-sourced protein is described. Pages 53-68 describe how to make the proteins of this invention, including a detailed description for the design of the consensus gene sequence and a

protocol for the retrieval of genes encoding native osteogenic sequences on pp. 53-60, and a detailed description for the rational design of novel, non-native osteogenic sequences on pp. 60-65, including the generic core amino acid sequence formulas on page 62. Examples of biosynthetic non-native proteins are presented on pp. 64-65. Methods for the recombinant production of native or biosynthetic non-native sequences are provided on pp. 66-68.

The Examiner further is directed to pp. 68-74, where methods for making a suitable device for testing the proteins of this invention are described, including a detailed description of the necessary characteristics for matrix materials and for device formulations.

Finally, the Examiner is directed to pp. 74-88 wherein Applicants describe how to test potentially useful proteins to identify proteins that are osteogenically (or chondrogenically) active. Specifically, on pp. 74-77 Applicants describe how to perform in vivo assays to test for cartilage or bone formation in a mammal using proteins falling within the generic sequences described. On pp. 77-88 Applicants detail the results of these assays performed using certain osteogenic proteins of the invention.

Using the methodology outlined in the specification, Applicants have identified native sequences encoding osteogenic proteins, including novel sequences and sequences not previously known to induce endochondral bone formation, and have successfully designed, expressed and tested a number of non-native, biosynthetic sequences and shown these to be osteogenically active.

Accordingly, the specification, in combination with the ordinary skill of those in the art, enables the artisan to produce any candidate sequence desired, and also teaches how to test a candidate sequence for activity. One can readily determine whether any given sequence falls within the claims. Accordingly, Applicants respectfully submit that the metes and bounds of the proteins of the invention are adequately enabled and described by the specification.

Rejection of the Claims Under 35 USC §112

The claims currently under consideration stand rejected under 35 USC §112, second paragraph, as being indefinite. The Examiner asserts that because the specification does not teach precisely what "X" may represent, the proper metes and bounds as to what may be embraced by the claims cannot be clearly ascertained. Applicants respectfully traverse this rejection, to the extent it is applied to the claims as amended.

Applicants respectfully submit that they adequately define "X" in the specification for the reasons detailed above, and that the claims accordingly are definite. Applicants' discovery of the amino acid residues and linear sequence necessary for bone (or cartilage) forming activity allows them to define their invention generically. Applicants' discovery allows them to identify and retrieve genes encoding novel osteogenic proteins, and to design and produce active, totally biosynthetic osteogenic proteins, e.g., COP5 or COP7, based on the critical core sequence. Accordingly, Applicants have claimed the invention generically as dimeric proteins comprising a pair of polypeptide chains having an amino acid sequence sufficiently duplicative of the amino acid sequence of the non-native biosynthetic sequences COP5 or COP7 such that, when the polypeptide chains are dimerized, disulfide-bonded and implanted in a mammal in

association with a matrix, the dimeric protein has a conformation capable of inducing endochondral bone formation. As amended, the pending claims also now so define Applicants' invention. The polypeptide chains also may be described by the generic sequence formulas presented on p. 62 of the specification and in dependent claims 28 and 29. Dependent claims 81 and 82 describe currently preferred embodiments of these generic sequences wherein the amino acids of the variable positions are selected from particular subsets of possible residues. These subsets are compiled from the known residues that appear at that position in the native sequences and non-native sequences identified or created to date, and which have been confirmed as osteogenically active.

Applicants submit the claimed, broad invention is adequately enabled by the specification, and that they are entitled to claim protection of sufficient breadth to cover the invention. To limit the claims narrower than the generic invention is to invite others to make minor modifications of any specific sequence claimed, using the knowledge provided by Applicants' specification, to create proteins that escape the coverage of the claims. Moreover, the courts hold that

"The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions." In re Sus 134 USPQ 301, 304 (1962).

Applicants respectfully submit that the claims, as amended, appropriately describe that subject matter which Applicants regard as their invention and that the specification is sufficient to enable one of ordinary skill in the art to make and use the invention without undue experimentation. In addition, while there may be specific sequences of amino acids falling within the

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generic sequences set forth in the claims which will be nonfunctional, Applicants submit that the teaching of the specification allows one of ordinary skill to make, assess the activity, and, if active, use any specific amino acid sequence within the generic sequence without undue experimentation. Moreover, the courts have held consistently that

"...it is not a function of the claims to specifically exclude either possible inoperative substances or ineffective reactant proportions." In re Dinh-Nguyen and Stenhagen, 181 USPQ 46, 48 (CCPA, 1974). And, "...[the] Patent Office has no concern over breadth of term....[I]ts only relevant concern should be over the truth of such assertion. First paragraph of 35 USC 112 requires nothing more than objective enablement. How such a teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." In re Marzocchi and Horton, 169 USPQ 367, 369, (CCPA, 1971).

Accordingly, Applicants respectfully submit that all of the pending claims, as amended, comply with the second paragraph of 35 USC §112. Specifically, the metes and bounds of the proteins embraced by the claims 22-26, 28, 29, 45, 50, 51, 81 and 82 are defined adequately by the specification and are ascertainable.

Objection to Recitation of Claim 46

The Examiner objects to the format of claim 46. In an effort to promote prosecution of this application, claims 46, 83 and 84 have been deleted herein and are not discussed further.

Provisional Rejection of Pending Claims Under Consideration Under 35 USC §101 Over Claims 1-19, 21 of USSN 660,162.

The pending claims under consideration are provisionally rejected under 35 USC §101 as claiming the same invention as that of claims 1-19 and 21 of USSN 660,162. USSN 660,162 has been refiled as a file wrapper continuation having application Serial No. 810,560.

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The pending claims under consideration in the instant application are drawn to osteogenic proteins comprising a pair of polypeptide chains each of which is less than about 200 amino acids in length and has a sequence sufficiently duplicative of the sequence of COP5 or COP7 such that the pair of polypeptide chains, when disulfide bonded to produce a dimeric species, has a conformation capable of inducing endochondral bone (or cartilage) formation in a mammal when implanted in the mammal in association with a matrix.

The claims of USSN 810,560 all are directed, in various ways, to a particular, novel dimeric osteogenic protein, one of whose subunits comprises OP-1, including analogs thereof, such as truncated or mutated forms and forms having varying glycosylation patterns or varying N-termini.

The test for same invention double patenting under 35 USC §101 is set out in In re Vogel, 164 U.S.P.Q. 619 (CCPA, 1970): if the claims of one patent could be literally infringed without infringing the claims of the other patent, then different inventions exist for double patenting purposes. The court in In re Vogel stated that "... by the same invention we mean identical subject matter." By way of example, the court stated that a claim reciting a "halogen" is not the same as a claim reciting "chlorine" because halogen is a broader term then the species chlorine.

The pending claims of the instant case have a different scope than those of the '560 application. In re Vogel, ibid. The instant claims are broader than the claims of the '560 application. Specifically, the instant independent claims are directed to dimeric osteogenic proteins wherein both subunits comprise an amino acid sequence sufficiently duplicative of the

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non-native biosynthetic sequences of COP5 or COP7. By contrast, the referenced claims of the '560 application require that the dimeric osteogenic protein comprise OP1 or an analog thereof as a subunit. Therefore, the claims of the present application could be infringed without infringing the claims of the '560 application. The reverse situation also holds. Thus, the present claims do not define the same invention as that claimed in USSN 810,560 as required for a proper rejection under 35 USC §101. Accordingly, Applicants respectfully request that the double patenting rejection under 35 USC §101 of the claims, as amended, be withdrawn.

Applicants further advise the Examiner that the subject matter of the '560 application has been combined with that of other pending applications, updated, and incorporated in a new continuation-in-part application, USSN 07/841,646, filed February 21, 1992. The '560 application accordingly will be allowed to go abandoned.

Applicants intend to maintain a line of demarcation between the instant case and the claims of '646 application to avoid same invention type double patenting by appropriately amending, as required, the claims of the '646 application. It is requested that the Examiner hold this rejection in abeyance until such time as prosecution of the '646 application commences.

Provisional Rejection of Pending Claims Under Consideration Under 35 USC §101 Over Claims 58-61 of USSN 232,630

The pending claims under consideration also stand provisionally rejected under 35 USC §101 as claiming the same invention as claims 58-61 of USSN 232,630. Applicants respectfully traverse this rejection. The '630 application has been expressly abandoned in favor of the '646 application identified above. A copy of the Notice of Express Abandonment is

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enclosed. Applicants intend to maintain a line of demarcation between the instant case and the claims of '646 application to avoid same invention type double patenting by appropriately amending, as required, the claims of the '646 application. Applicants request that this rejection also be held in abeyance pending the start of prosecution of the '646 application.

Provisional Rejection of Pending Claims Under Consideration under 35 USC §101 over claim 23 of USSN 569,920.

The pending claims under consideration also stand provisionally rejected under 35 USC §101 as claiming the same invention as claim 23 of USSN 569,920. Applicants respectfully traverse this rejection. The '920 application also now has been expressly abandoned in favor of the '646 application. A copy of the Notice of Express Abandonment for USSN 569,920 is enclosed. Applicants intend to maintain a line of demarcation between the instant case and the claims of '646 application to avoid same invention type double patenting by appropriately amending, as required, the claims of the '646 application. Applicants respectfully request that this double patenting rejection be held in abeyance pending the start of prosecution of the '646 application.

Finally, Applicants respectfully request that the Examiner consider whether any pending claim in the instant application is deemed obvious in view of any of the claims of U.S. Patent No. 4,968,590 or any of the allowed claims of co-pending USSN 579,865. Applicants believe the claims under consideration in the instant case are unobvious over the allowed claims of USSN 579,865 and the issued claims of U.S. Pat. No. 4,968,590. Applicants assume the Examiner agrees as he handled prosecution of both previously filed applications and therefore is familiar with their claims. However, if, upon review, the Examiner considers a double patenting rejection to be in order, Applicants request that it be asserted so that they can resolve the issue.

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On the basis of the above amendments and remarks, reconsideration and allowance of the application and the claims is requested.

Respectfully submitted,

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Dated: 4/27/92

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